NKDEP
National Kidney Disease Education Program

Suggestions for Laboratories

Revised December 2005

This document has been developed by the National Kidney Disease Education Program (NKDEP) to provide clinical laboratories with information that can help them:

- accurately report estimated glomerular filtration rate (GFR) based on serum creatinine;
- understand the NKDEP initiative to standardize the measurement of serum creatinine; and
- communicate with healthcare providers about the implications of new serum creatinine values that will result from the creatinine standardization initiative.

Estimating GFR

The NKDEP strongly encourages clinical laboratories to automatically report estimated GFR whenever serum creatinine is ordered. An estimated GFR from serum creatinine is a practical way to identify people with chronic kidney disease (CKD) who might otherwise go untreated, and to monitor those with risk factors for CKD—i.e., diabetes, hypertension, cardiovascular disease, or family history of kidney disease.

In adults, age 18 years and older, the MDRD (Modification of Diet in Renal Disease) Study equation has been shown to be reliable in estimating GFR from serum creatinine, when the patient's age, sex, and race are also known.[1,2] Use of the MDRD equation to estimate GFR is the best means currently available to more appropriately utilize serum creatinine values as a measure of renal function. The MDRD equation has been validated in predominantly white and African-American populations with impaired renal function. Efforts are now underway to validate the MDRD equation in more diverse populations including Hispanics, people with diabetes, and people with normal renal function.

IMPORTANT NOTE: The NKDEP recommends using one of two MDRD equations, depending on whether or not serum creatinine methods have been calibrated to be traceable to an isotope dilution mass spectrometry (IDMS) reference method. The two MDRD equations include the original *conventional calibration MDRD equation*, and the recently developed *IDMS-traceable MDRD equation* (for use by those clinical laboratories that are using creatinine methods that have been calibrated to be traceable to IDMS).

- Clinical laboratories using creatinine methods that have not yet been recalibrated to be traceable to IDMS should continue using the original conventional calibration MDRD equation.
- Clinical laboratories using creatinine methods that have already been recalibrated to be traceable to IDMS should use the recently developed IDMS-traceable MDRD equation and coordinate this use with method recalibration.

Conventional Calibration MDRD Equation

NOTE: This equation should be used only with those creatinine methods that have not been recalibrated to be traceable to IDMS. If you have any question about the traceability of the calibration for the creatinine method in use by your laboratory, NKDEP recommends that you contact the reagent and/or calibrator manufacturer for assistance.

The equation requires **four variables:**

- Serum, or plasma, creatinine (S_{cr})
- Age in years (18 years or older)
- Sex
- Race (African American or not)

When S_{cr} is in mg/dL (conventional units):

GFR (mL/min/1.73 m^2) = 186 x $(S_{cr})^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.210 if African American)

When S_{cr} is in µmol/L (SI units):

GFR (mL/min/1.73 m^2) = 186 x $(S_{cr}/88.4)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.210 if African American)

IDMS-Traceable MDRD Equation[3]

NOTE: This equation should be used only with those creatinine methods that have been calibrated to be traceable to IDMS. If you have any question about the traceability of the calibration for the creatinine method in use by your laboratory, NKDEP recommends that you contact the reagent and/or calibrator manufacturer for assistance.

The equation requires **four variables:**

- Serum, or plasma, creatinine (S_{cr})
- Age in years (18 years or older)
- Sex
- Race (African American or not)

When S_{cr} is in mg/dL (conventional units):

GFR (mL/min/1.73 m^2) = 175 x $(S_{cr})^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.210 if African American)

When S_{cr} is in µmol/L (SI units):

GFR (mL/min/1.73 m^2) = 175 x $(S_{cr}/88.4)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.210 if African American)

PT/EQA Implications

As laboratories make the transition from conventionally calibrated creatinine methods to IDMS-traceable methods, PT/EQA providers will need to make changes in participant grading to account for bimodal distributions of results.

The NKDEP is collaborating with PT/EQA providers and IVD manufacturers to ensure appropriate grading during this transition (which is expected to occur during 2006-2007) so that laboratories do not fail a PT/EQA challenge as a result of recalibration of their creatinine method by a reagent/calibrator manufacturer. PT/EQA providers will be asked to create new instrument/method peer groups that reflect the calibration status (conventional or IDMS-traceable) of the various serum and urine creatinine methods used by participant laboratories. Participating laboratories will need to choose the correct instrument/method peer group for the respective creatinine method and calibration currently in use by their laboratory. NKDEP recommends that, for purposes of method classification and peer grouping for proficiency testing, if the laboratory has any doubts about the appropriate classification of their creatinine method and its associated calibration, they should contact the reagent and calibrator manufacturer(s).

The NKDEP also encourages laboratories to participate in a regularly recurring PT/EQA program that uses commutable serum materials with target values traceable to IDMS reference measurement procedures. Such a program will allow individual laboratories and IVD manufacturers, on an ongoing basis, to assess the performance of routine clinical laboratory methods for creatinine, the success of manufacturers' accuracy transfer processes, and the laboratory standardization program.

Reporting Values for Estimated GFR

Since a patient's race is often not available to clinical laboratories, and because mixed ethnicity can make it difficult to classify a patient's race, a general recommendation is to report, for all creatinine results, the estimated GFR values for both African Americans and non-African Americans (see Sample Reports following). Note that the equation does not require weight or height because the result is reported normalized to 1.73 m^2 body surface area, which is an accepted average adult body surface area.

The NKDEP recommends reporting serum creatinine values in mg/dL to two decimal places (e.g., 0.95 mg/dL); and reporting values in µmol/L to the nearest whole number (e.g., 84 µmol/L). This reporting recommendation will reduce rounding errors that may contribute to imprecision in the estimated GFR value.

The NKDEP presently recommends reporting estimated GFR values ***above 60 mL/min/1.73 m²*** simply as ">60 mL/min/1.73 m^2", not as an exact number. For values ***60 mL/min/1.73 m² and below,*** the report should give the numerical estimate rounded to a whole number (e.g., "32 mL/min/1.73 m^2"). There are 3 reasons for this recommendation:

1. The equation has been most extensively evaluated in people with some degree of renal insufficiency.
2. Inter-laboratory differences in calibration of creatinine assays, and the imprecision of the assays, have their greatest impact in the near-normal range and therefore lead to greater inaccuracies for values >60 mL/min/1.73 m^2.[4]
3. Quantification of GFR below 60 mL/min/1.73 m^2 has more clinical implications for classification of kidney function than above that level.

Sample Reports

NOTE: If your printing system does not allow for superscripts, we recommend reporting mL/min/1.73 "square meters" or "m^2."

The following sample reports for estimated GFR (GFRest) have been developed using the Conventional Calibration MDRD Equation:

Sample report for a 63-year old woman
Creatinine = 1.82 mg/dL
GFRest if African American = 36 mL/min/1.73 m^2
GFRest if non-African American = 30 mL/min/1.73 m^2

Sample report for a 62-year old man
Creatinine = 1.35 mg/dL
GFRest if African American = >60 mL/min/1.73 m^2
GFRest if non-African American = 57 mL/min/1.73 m^2

Sample report for a 55-year old man
Creatinine = 1.07 mg/dL
GFRest if African American = >60 mL/min/1.73 m^2
GFRest if non-African American = >60 mL/min/1.73 m^2

The decision limits for GFRest can be indicated as >60 mL/min/1.73 m^2 because numeric values are not provided at higher values.

Communicating with Healthcare Providers

The NKDEP encourages clinical laboratories to communicate with healthcare providers—including pharmacists—about the clinical issues associated with recalibrating serum creatinine measurement to be traceable to IDMS.

Healthcare providers should be informed that:

- The serum creatinine reference interval will change, in most cases, to lower values.
- Creatinine clearance values based on measured serum and urine creatinine results may change, and a new reference interval and interpretive criteria may need to be established. The effect on measured creatinine clearance will vary depending on the procedure used to calibrate serum and urine measurements.
- For most patients, an estimated GFR using the MDRD equation is more accurate than a creatinine clearance calculated from serum and urine measurements. Therefore, NKDEP recommends not performing a measured creatinine clearance procedure for adults except when the patient's basal creatinine production is expected to be very abnormal, such as patients of extreme body size or muscle mass (e.g., morbidly obese, severely malnourished, amputees, paraplegics or other muscle-wasting diseases) or with unusual dietary intake (e.g., vegetarian, creatine supplements).
- The clinical laboratory should notify the pharmacy and drug prescribers to inform them of the expected magnitude of change in serum creatinine values, and whether the creatinine clearance measured from serum and urine will be affected by the change.

- Following implementation by IVD reagents/calibrators/systems manufacturers of revised calibrations (traceable to IDMS) for serum creatinine methods, other creatinine clearance and/or GFR estimating equations such as Cockcroft-Gault, Schwartz, or Counahan-Barratt will give values that, in most cases, are higher than the values obtained before creatinine method recalibration.
- The uncertainty in estimating GFR in children is greater than in adults, and an alternate assessment of renal function should be used.

The NKDEP encourages IVD manufacturers to provide the necessary information to clinical laboratories describing the relationship between serum and urine creatinine results when measured with IDMS-traceable methods compared to the results obtained using conventional calibration.

Next Steps The Creatinine Standardization Program

The NKDEP Laboratory Working Group is about to launch the Creatinine Standardization Program to assist IVD manufacturers and clinical laboratories to address inter-laboratory variation in creatinine assay calibration and provide more accurate estimates of GFR. At the present time, traceability to IDMS reference methods can be established by collaborating with a reference measurement laboratory offering GC-IDMS reference method testing services. The JCTLM website (www.bipm.fr/utils/en/xls/jctlm_listl.xls) provides information on approved reference measurement procedures and lists the submitting laboratories (three GC-IDMS methods are currently listed). It is anticipated that a higher throughput LC-IDMS reference measurement procedure may be approved in 2006.

The National Institute for Standards and Technology (NIST) is in the process of developing a new reference material (SRM 967) based on off-the-clot frozen serum pools [two levels, approximately 71 µmol/L (0.80 mg/dL) and 354 µmol/L (4.00 mg/dL)]. Value assignment by GC-IDMS and LC-IDMS and validation of commutability with a panel of native serum samples for a group of routine clinical methods for serum creatinine are expected to be completed in early 2006. Availability of this SRM will provide a practical reference material for use in establishing traceability to IDMS creatinine methods. NKDEP collaborated with NIST and the College of American Pathologists to develop SRM 967 and the CAP LN24 Creatinine Accuracy Calibration Verification/Linearity Survey. The materials for these two products were prepared by the same process, and CAP LN24 will be validated for commutability along with the NIST SRM. In addition to addressing inter-laboratory variation in creatinine assay calibration, the NKDEP Laboratory Working Group is also encouraging IVD manufacturers to improve the precision of serum creatinine measurements at lower concentrations. This will enable clinical laboratories to provide more accurate estimations of GFR in the range greater than 60 mL/min/1.73 m^2 and in children.

The most current information about the NKDEP Creatinine Standardization Program, other resources for laboratory professionals, and a link to subscribe to free email updates about relevant topics are available at **www.nkdep.nih.gov/labprofessionals**. Updates will be made regularly as the standardization program develops.

Contact Info

For assistance, please contact Elisa Gladstone (tel: **301-435-8116**; email: **gladstoneE@mail.nih.gov** with the National Kidney Disease Education Program.

References

1) Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003; 139:137-47.
2) Manjunath G, Sarnak MJ, Levey AS. Prediction equations to estimate glomerular filtration rate: an update. *Curr Opin Nephrol Hypertens* 2001; 10:785-92.
3) Abstracts Supplement of the Journal of the American Society of Nephrology, Vol 16, 69a, Copyright © 2005 by American Society of Nephrology. Research was presented during ASN's 38th Annual Meeting & Scientific Exposition in Philadelphia, PA.
4) Coresh J, Astor BC, McQuillan G, et al. Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. *Am J Kidney Dis* 2002; 39:920-9.